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NEPHROLOGY FORUM

Complications in hemodialysis: An overview

Principal discussant: J. MICHAEL LAZARUS

Harvard Medical School and Peter Bent Brigham Hospital, Boston, Massachusetts

Case presentation

A 23-year-old man developed end-stage renal failure secondary to lupus glomerulonephritis. Systemic lupus erythematosus (SLE) was diagnosed 4.5 years ago on the basis of typical clinical and laboratory findings. His renal function was initially normal, but 6 months later moderate renal insufficiency was noted when he was hospitalized for severe hypertension and cardiac failure. A Scribner shunt was placed to permit management of fluid overload by dialysis, but the shunt could not be preserved because a *Staphylococcus aureus* infection developed at the shunt site. Renal biopsy revealed severe, diffuse proliferative glomerulonephritis consistent with lupus. The patient was treated initially with high doses of prednisone and with diazoxide, propranolol, furosemide, hydralazine, and methyldopa. His blood pressure was controlled on this regimen and his serum creatinine fell from 5.0 mg/dl to approximately 3.8 mg/dl. The dose of prednisone was gradually reduced to 10 mg every other day. Treatment with large doses of propranolol, hydralazine, methyldopa, thiazides, and furosemide failed to control his blood pressure over the next few months; his cardiomegaly progressed and cardiac failure worsened.

Two and one-half years ago, minoxidil was added to his antihypertensive regimen, and his diastolic blood pressure was reduced to between 100 and 110 mg Hg; his renal function deteriorated, however. The addition of cyclophosphamide to the regimen stabilized his renal function at a serum creatinine of approximately 4.5 mg/dl. The cyclophosphamide was discontinued 1.5 years ago, however, because the patient developed pancytopenia; the serum creatinine, which had increased to approximately 5.5 mg/dl after the drug was discontinued, temporarily stabilized at this level.

One year ago, during a hospitalization for pneumococcal pneumonia, the patient's renal function further declined; the serum creatinine rose to 8.5 mg/dl and the BUN increased to 150 mg/dl. A pericardial effusion developed and failed to respond to daily hemodialysis (via a second Scribner shunt) using regional administration of heparin; the effusion increased in size, cardiac tamponade occurred, and pericardiocentesis was required. An anterior pericardiectomy was performed to avert recurrent tamponade. The pericardial fluid was grossly bloody (hematocrit 25%) and did not contain autoantibodies. Pathologic examination revealed fibrinous pericarditis. At no time before or during the episode of pericarditis was any clinical or laboratory evidence of "active" SLE apparent.

Following the patient's hospitalization for pericarditis, hemodialysis was complicated by recurrent problems of vascular access. The second Scribner shunt was removed because of another *S. aureus* infection, and a third shunt was inserted but functioned only transiently. An effort was made to convert this shunt to an arteriovenous fistula, but the fistula clotted before it could be used. A fourth shunt was inserted, but it too became a focus of staphylococcal infection and was removed. For one month following removal of the fourth shunt, hemodialysis was performed every 5 days via a femoral vein catheter. During this difficult period, the patient's compliance with therapy was poor and his diastolic blood pressure remained at 100 to 110 mm Hg.

Four months ago, a Gortex® graft was interposed between the brachial artery and cephalic vein; since then the patient has been dialyzed twice weekly, and compliance with all aspects of therapy has improved markedly. At present, he has no symptoms or signs of SLE or cardiac failure.

His most recent physical examination showed mild facial puffiness and grade 2 hypertensive changes in the optic fundi. The point of maximal impulse was at the anterior axillary line in the 7th intercostal space; a left ventricular heave was prominent. A systolic rub and S3 and S4 gallops were present. The chest was clear, and the patient had no jugular vein distention, hepatomegaly, or edema. The site of the Gortex® graft in the left arm was well healed, was uninfected, and had a prominent thrill. No arthritis, rash, lymphadenopathy, or alopecia were present.

The current medical regimen of minoxidil (40 mg/day), propranolol (640 mg/day), and furosemide (320 mg/day), has maintained the patient's blood pressure at 160/80 to 160/100 mm Hg. The patient also takes digoxin, 0.125 mg, every other day, aluminum hydroxide, folic acid, and multivitamins; the prednisone has been discontinued. He receives neither iron nor androgens. His daily urinary output is 500 to 800 cc.

Predialysis values for BUN and serum creatinine are approximately 130 mg/dl and 13.0 mg/dl respectively. The anti-DNA titer is normal and the serum complement mildly depressed. The hematocrit is 20%. The patient has received a total of 27 transfusions, 12 since the initiation of hemodialysis. A chest x-ray and echocardiogram show marked left ventricular hypertrophy but

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no pericardial fluid. He has returned to school to study electronic repair and is currently considering renal transplantation.

Discussion

DR. J. MICHAEL LAZARUS *(Nephrology Division, Peter Bent Brigham Hospital, and Associate Professor of Medicine, Harvard Medical School, Boston, Mass.):* This patient with systemic lupus erythematosus and renal failure has experienced multiple complications including severe and persistent hypertension, uncontrolled congestive heart failure, pancytopenia and infection secondary to immunosuppressive therapy, multiple shunt failures with infection, and pericarditis requiring pericardiectomy. These sequelae are unusually severe but demonstrate the typical complications experienced by patients undergoing chronic hemodialysis. In my opinion, the difficulties encountered, save those due to access failure, are not related to hemodialysis per se, but rather to lupus erythematosus, persistent uremia, and drug therapy.

In the subsequent discussion, I will divide complications of hemodialysis into those that are (*1*) consequences of the usual dialysis procedure; (*2*) mechanical, iatrogenic, or both; and (*3*) manifestations of persistent or incompletely treated uremia. Other treatment options such as peritoneal dialysis and renal transplantation will not be discussed, but obviously these play an important role in the management of complications associated with hemodialysis.

Medical threapy has produced few treatments as dramatically lifesaving as dialysis. Many physicians, particularly nonnephrologists, aware only of the dramatic and beneficial effects of dialysis, have become nonchalant about hemodialysis. Like all forms of therapy, hemodialysis is a double-edged sword that can have severe, adverse consequences, including death. Knowledge of the potential hazards of treatment thus is mandatory to estimate accurately the risks and benefits of hemodialysis.

Consequences of the usual hemodialysis procedure

Hemodialysis can be viewed as two distinct phenomena: clearance and ultrafiltration. Conceptual separation of clearance or diffusion and ultrafiltration is necessary for understanding the dialysis procedure and developing the proper approach to individual patients. One can utilize a rapid blood flow rate and large surface area dialyzer to increase or maintain clearance, yet minimize fluid removal either by using low hydrostatic pressure or replacing a quantity of fluid equal to that removed. On the other hand, one can minimize clearance utilizing a small dialyzer with a slow blood flow rate while using maximum hydrostatic ultrafiltration to achieve greater fluid removal.

Changes in vascular volume. The most critical change that occurs with hemodialysis is reduction of extracellular volume by ultrafiltration. I believe that failure to control extracellular volume adequately is the major long-term contributor to morbidity and mortality in patients with end-stage renal disease. Insidious visceral engorgement, third-space collections, and pulmonary edema result from fluid overload. Hypertension in dialysis patients is also usually volume dependent [1, 2], and the high incidence of cardiovascular disease in uremic patients largely results from the persistent fluid overload and resulting hypertension [3]. Therefore, efforts at reducing vascular volume to its lowest possible point, i.e., "dry weight," are very important in these patients.

Several factors influence the likelihood of complications during fluid removal by dialysis: (*1*) volume of the dialyzer and blood lines; (*2*) compliance of the dialyzer, that is, the degree of expansion of the blood compartment with an increase in resistance to flow; and (*3*) magnitude of ultrafiltration. A large extracorporeal circulation, a highly compliant dialyzer, and an increased ultrafiltration coefficient are more likely to lead to hypotension than is a small surface area dialyzer with a low ultrafiltration coefficient. Newer dialyzing membranes allow a degree of ultrafiltration such that fluid can be removed from the vascular compartment faster than it can be replenished from interstitial and intercellular spaces. Other factors such as uremic autonomic neuropathy [4, 5], hormonal changes, and myocardial disease complicate efforts at reducing vascular volume. The potential adverse effects of antihypertensive medications as well as changes in osmolality and blood acetate concentration also should be assessed when one attempts ultrafiltration.

Total separation of diffusion and ultrafiltration does not occur in standard dialysis because blood flow is necessary to generate venous pressure and also because of the effect of ultrafiltration on convective diffusion, i.e., the movement of solutes that results from movement of the solvent. So called "sequential dialysis" is a procedure in which ultrafiltration and clearance are separated [6]. Ultrafiltration occurs across a high-flux dialysis membrane without dialysis flow for short periods; then dialysis is begun and clearance occurs, but no fluid removal

is attempted. Recent investigations have indicated that this separation of diffusion and ultrafiltration might allow a more stable dialysis and facilitate the removal of larger quantities of fluid [7]. Obviously, reduction of extracellular volume below some critical point, regardless of technique, will lead to hypotension and its consequences.

The benefits of fluid removal must be weighed against the potential hazards. Extracting large quantities of fluid in one treatment can lead to transient episodes of hypotension and severe cardiovascular and cerebral sequelae. In the young, relatively well, hypertensive patient, such as the patient presented today, one should be aggressive in removing fluid; in the elderly patient with cerebrovascular or cardiovascular disease, efforts at reaching the patient's dry weight must be tempered. It is important that the physician encourage minimum weight gains between treatments so that only small reductions in volume will be necessary with each dialysis. Generally, if one can discontinue antihypertensive medications, blood pressure remains more stable during dialysis and extracellular fluid is more easily removed. Indeed, antihypertensive medication often then becomes unnecessary. In the small percentage of patients whose hypertension does not respond to a reduction in extracellular volume, antihypertensive medication must be continued, but drug therapy should be withheld for 4 to 6 hours preceding the dialysis procedure so that the vasodilatory effect of these drugs will be minimized during dialysis.

Electrolyte and osmolar shifts. Abrupt changes in the concentration of sodium, potassium, and calcium during hemodialysis can induce serious consequences. Diffusion or clearance of electrolytes and other substances can create changes in intra- and extracellular concentrations and can alter osmolality. The rate of diffusion or clearance depends on the surface area of the dialyzer, characteristics of the membrane, blood and dialysate flow rates, and the concentration gradients between blood and dialysate.

Most dialysate solutions have sodium concentrations between 130 and 140 mEq/liter. The lower sodium concentrations are used to remove sodium and thereby reduce blood pressure. However, patients frequently develop mild hyponatremia, a chemical disorder that might be related to the development of side effects such as muscle cramps and dialysis disequilibrium. Severe dialysis disequilibrium is manifested by marked mental and psychiatric changes and grand mal seizures; a mild disequilibrium occurring after dialysis produces headache, fatigue, and lethargy [8, 9]. Rapid changes in the concentration of urea or other unidentified osmotically active agents (idiogenic osmoles) and changes in the pH of the central nervous system contribute to the pathogenesis of this syndrome [9, 10]. The rate of change of serum sodium, urea, or other substance is probably more important than is the quantity of any substance removed. The syndrome usually can be prevented by avoiding prolonged and efficient dialysis, particularly when the blood urea nitrogen is markedly elevated. Gentle correction of the uremia can be accomplished by dialyzing for brief periods at first, maintaining low blood flows, and using a dialyzer with a small surface area. Of course, this approach results in a slower resolution of the uremia and its attendant complications. Intravenous osmotic agents such as mannitol or dextrose reduce the intensity of osmolar change and are believed by some to be effective in preventing muscle cramps and disequilibrium [11]. Use of the ideal sodium concentration in the dialysate should strike a balance: it should remove sodium while obviating symptoms of hyponatremia.

The most critical electrolyte shift in patients undergoing hemodialysis involves potassium. Hyperkalemia often occurs in patients with advanced renal failure. One can lower serum potassium by utilizing a dialysate potassium concentration between 1.5 and 3.0 mEq/liter. In the patient with cardiac failure who takes digitalis, the patient with coronary disease and an irritable conduction system, or the small, elderly patient whose dietary intake is inadequate, a low potassium concentration in the dialysate can lead to transient hypokalemia and severe rhythm disturbances. Such patients require a higher potassium concentration in the dialysate. Dialysate potassium concentration can be manipulated readily in the dialyzer assigned to a single patient. In central delivery systems, however, all patients undergo dialysis against a bath of the same composition. To avoid hyperkalemia in many of the patients dialyzed on a central system, one must use a dialysate potassium concentration of 3 mEq/liter or less. At these relatively low potassium concentrations, hypokalemia occurs transiently in some patients, and arrhythmias can develop in the susceptible groups described before, but careful oral administration of small quantities of potassium usually can solve this problem. A patient with an extremely high serum potassium level probably should not be dialyzed initially against a very low dialysate potassium concentration because, in my

experience, abrupt and large changes in serum potassium can induce cardiac rhythm disturbances. A preferable approach to such a patient is multiple bath changes with graded lowering of the potassium concentration of the dialysate. Finally, we should remember that serum calcium levels are altered by dialysate calcium and that the relationship between calcium and potassium as well as the absolute serum levels of these electrolytes are important factors in cardiac activity [12].

Acetate accumulation. In the early 1960s, acetate was developed as a dialysate buffer to avoid the use of complicated systems containing bicarbonate and bubbled carbon dioxide [13]. An acetate buffer can cause transient decreases in serum bicarbonate, however [14, 15]. Sargent and Gotch recently demonstrated that patients treated for long periods with acetate-buffered dialysate become bicarbonate depleted [16]. In addition, transient acetate accumulation occurs during and immediately after dialysis in a significant percentage of patients [17, 18]. Although the exact cause of this accumulation is unknown, it might result from (*1*) administration of acetate at a rate exceeding metabolic clearance; (*2*) a reduction, because of circulatory insufficiency, of acetate delivery to active metabolic sites; or (*3*) defective acetate metabolism [18, 19]. The acetate ion has been cited as a cause of myocardial depression [20, 21] and cardiovascular instability in seriously ill patients [22]. Simpler systems for the delivery of bicarbonate dialysate recently have been developed, and investigation is underway to evaluate further the benefits of bicarbonate as the source of alkali in patients undergoing hemodialysis.

Anticoagulation. Abnormalities of platelet factor III activity and platelet adhesiveness due to uremia can be reversed by hemodialysis [23]. Bleeding remains a risk, however, because systemic administration of heparin is necessary in carrying out extracorporeal circulation. Also, many dialysis patients are treated with warfarin, aspirin, and antiplatelet drugs to help preserve the patency of arteriovenous shunts and fistulas. These agents can induce a variety of bleeding complications including gastrointestinal hemorrhage; bloody pericardial, pleural, and joint effusion; subdural hematoma; retroperitoneal hematoma; ocular and retinal hemorrhage; and increased menstrual flow [24]. The use of invasive diagnostic and therapeutic procedures shortly before or after hemodialysis has been associated with unusual hemorrhagic complications. If possible, such procedures should be deferred until the effects of heparin have dissipated.

Shunt and fistula problems. The most frequent causes of hospitalization in patients on maintenance hemodialysis are replacement, repair, removal, or treatment of infection of an arteriovenous (AV) shunt or fistula (Table 1). The AV shunt is now used primarily when a patient is expected to require dialysis for only days or a few weeks; the AV fistula, created either from a native vein or with a prosthesis, is usually reserved for long-term care. Although AV shunts have a high incidence of thrombosis and infection, they can be used immediately and do not require venipuncture. The Seldinger technique of percutaneous catheterization of major vessels, described almost 20 years ago [25], recently has gained renewed interest as a means of access for hemodialysis. Femoral vein catheterization currently is used most frequently [26], but subclavian vein catheterization also has been described [27]. We prefer vein catheterization rather than an A-V shunt because it can be used immediately, preserves arteries and veins, does not involve a surgical procedure, and is relatively safe. Complications, although unusual, include retroperitoneal hematoma, injuries to the adjacent artery with hemorrhage, and infection if an unattended catheter is left in place [28, 29]. Femoral vein catheterization is probably the procedure of choice for patients with uncomplicated acute renal failure and can provide a temporary approach in patients on maintenance dialysis who are awaiting a more permanent type of access.

An AV fistula created with the patient's own blood vessels provides the most desirable access and is least susceptible to infection and thrombosis [30]. However, suitable fistulas cannot always be created because of previous trauma to the venous system from intravenous therapy or because of compromised arterial flow. Prosthetic AV fistulas can be used when native vessels are not suitable. These implants produce thrombosis and infection less often than does the AV shunt but more often than the native vein fistula [30, 31]. The prosthetic AV fistula can be easily placed even when native vessels are not available. Because this situation

Table 1. Complications of shunts and fistulas

Repeated thromboses requiring multiple operations
Vascular compromise and vascular "steal"
Infection
Local
Endarteritis with septicemia and septic emboli
Aneurysm with rupture
Increased cardiac output
Carpal tunnel syndrome
Recirculation yielding inadequate dialysis

occurs often, the prosthetic AV fistula is the most commonly used means of access to the circulation.

Access to the circulation is clearly the Achilles heel of chronic hemodialysis; the patient described today had four access operations before a successful AV fistula could be created. Multiple surgical procedures, prolonged hospitalization, and depletion of access sites cause much anxiety and stress in hemodialysis patients. In some, particularly elderly or diabetic patients with previously compromised arterial flow, reduction of blood supply leads to tissue ischemia and occasionally to amputation of a digit or extremity. This problem is so severe in diabetic patients that many vascular surgeons avoid placing a shunt or fistula in the leg. A less common complication is the "steal syndrome," which occurs when the distal radial artery has not been ligated and blood flows from the ulnar artery to the palmar arch into the fistula [32]. Upper arm AV fistulas also have been reported to cause the steal syndrome [33]. The AV shunt or fistula increases cardiac output approximately 5% to 8%, and this effect must be considered in patients who have borderline cardiac function. The advantages of controlling fluid volume and hypertension through hemodialysis usually outweigh the disadvantages of increased cardiac output.

Recirculation is the phenomenon of an inappropriate mixture of venous and arterial blood in the fistula, such that a "short circuit" occurs in the systemic circulation. Recirculation results when a single needle is used or when two needles are placed close together in a fistula that has a high pressure due to resistance to outflow. The degree of recirculation can be calculated by determining the BUN or serum creatinine from specimens taken simultaneously from the arterial line (A), venous line (V), and a distant peripheral source (P):

$$\frac{P - A}{P - V} \times 100 = \% \text{ recirculation}$$

Generally, a good fistula with proper cannulation has a recirculation of less than approximately 10%.

Infection is a common and serious complication in the patient with a shunt or fistula. The most common type of infection is confined to the access site, but some patients develop infective endarteritis with septicemia and septic emboli. *Staphylococcus aureus* is the most common pathogen [30, 34]. Organisms presumably gain access to the circulation either from local infections or as a consequence of manipulation of the fistula or shunt in conjunction with dialysis. Endarteritis in dialysis is manifested by fever, and peripheral emboli; the patient's blood cultures are positive. Endarteritis mimics bacterial endocarditis, which also can result from infection of the access site. A *changing* heart murmur or other evidence of valve involvement, e.g., an abnormal echocardiogram, is sometimes the only clue for differentiating endocarditis from endarteritis. If treated early and vigorously, the prognosis of septicemia associated with fistulas and shunts is favorable [30, 34]. Treatment should be given for at least one week for local infections and for as long as two months for septicemia, septic emboli, or endocarditis. When septicemia persists, removal of the prosthesis might become necessary. The use of newer prosthetic materials such as polytetrafluoroethylene initially seemed to offer decreased rates of infection [35]; however, our experience indicates that thrombosis and infection are continuing problems [36].

It is extremely important that a native vein fistula be created before the patient becomes overtly uremic and before the veins are repeatedly traumatized by venipuncture or intravenous infusions. In the patient with progressive renal failure, the surgical procedure should be performed when the serum creatinine reaches 6 to 8 mg/dl so that the fistula will have sufficient time to enlarge before it is needed. Similarly, early placement of a prosthetic fistula is also important in allowing time for full healing and resolution of edema before use. In my experience, early placement is the most important factor in achieving prolonged survival of fistulas, and it probably would have avoided some of the access problems in the patient presented.

Mechanical and iatrogenic complications of hemodialysis

Complications that can result from equipment failure or errors by physicians and nurses are listed in Table 2. Air embolus and the consequences of improper composition of the dialysate (e.g., hemolysis and extreme changes in tonicity) were devastating complications in the past, but improved automated equipment and safety features largely eliminated these problems. Hemolysis can occur from inadequate water treatment or contamination of the dialysate [37, 38]. Other clinical problems such as dementia, hypertension, and sudden death can result from dialysate contamination with substances such as aluminum, calcium, and fluoride. Contamination can be prevented by the use of a deionizer, a reverse-osmosis device, or both [39–41]. Toxic chemicals such as diethylthalate and poly-

Table 2. Mechanical and iatrogenic complications of hemodialysis

Air embolus
Acute hemorrhage
Dialyzer leak
Disconnected shunt
Acute rupture of fistula (aneurysm)
Hemolysis
Dilute dialysate
Copper contamination
Chloramine, nitrate, formaldehyde contamination
Overheated dialysate
Acute hypernatremia
Contaminated dialysate
Bacterial
Trace elements or compounds in untreated water
Fluoride
Calcium
Magnesium
Insecticides
Aluminum
Synthetic material intoxication
Membrane-mediated pulmonary dysfunction
Deficiency states
Folate
Soluble B vitamins
Protein
Caloric
Unknown

vinyl chloride can be leached from membranes, dialyzer shells, or blood lines [42] and have been suggested as causes of cardiotoxicity [43] and necrotizing dermatitis [44]. Considering the long-term and massive exposure to synthetic dialysis materials, a significant toxic effect has yet to be convincingly documented; however, concern about toxicity persists.

The precipitous drop in the leukocyte count during hemodialysis is thought to result from activation of the complement system during exposure of blood to dialysis membranes. Leukocyte accumulation in the pulmonary vasculature has been held responsible for the pulmonary hypertension and hypoxemia that occur in some patients [45]. A fall in PaO_2 also might be related to hypoventilation induced by the hypocapnia that results from a loss of carbon dioxide during dialysis [46]. Whatever the cause, oxygen should be administered during dialysis to acutely ill patients whose clinical course might be compromised by mild hypoxemia.

The need to replace folate and B vitamins lost across the dialyzing membrane has been recognized for many years. Amino acid loss also can be considerable, and negative nitrogen balance can result if protein intake is inadequate in the patient on maintenance dialysis [47]. Carbohydrate-free dialysate, used in some units to reduce bacterial contamination, can lead to a loss of calories, which in turn can stimulate gluconeogenesis [48]. Other deficiency syndromes already might exist in an unrecognized form, and still others might be induced when membranes with enhanced clearance and ultrafiltration capacities become widely employed.

Persistent uremia

It is likely that some complications of uremia persist simply because of the inadequacy of current dialysis therapy. Table 3 lists some of these sequelae. Clearly, dialysis is not a total replacement for renal function. Determination of the adequacy of dialysis is a highly personalized judgment that depends on a combination of clinical and chemical findings. Measurement of BUN, serum creatinine, nerve conduction velocity, or any isolated test cannot determine proper treatment. Patient noncompliance often undermines adequate treatment, but recirculation, inadequate access, and failure to increase the dialysis regimen in the patient with an increased catabolic rate are other causes for failure of therapy. Institution of current optimal therapy can lead to resolution or improvement of most of the problems listed in Table 3.

Variable degrees of anemia persist in most patients undergoing maintenance dialysis [49–51]. Although this normochromic, normocytic anemia primarily results from decreased erythropoiesis, other factors including endogenous hemolysis, low-grade blood loss, iron deficiency, and folate deficiency also might contribute. Anemia is probably the principle cause of the fatigue and lethargy frequently experienced by these patients. The major hazard, however, is accentuation of cardiovascular or cere-

Table 3. Possible complications of persistent uremia

Anemia
Infection
Pericarditis
Atherosclerotic cardiovascular disease
Secondary hyperparathyroidism
(metabolic bone disease, vascular and visceral calcification)
Encephalopathies
Uremic encephalopathy
Disequilibrium
"Dialysis dementia"
Subdural hematoma
Chemical abnormalities
Hyperlipidemia
Acidosis
Hyperuricemia
Hypermagnesemia
Hyperamylasemia
Azotemia
Peripheral neuropathy

brovascular symptoms. A sustained high cardiac output can contribute to the development of cardiovascular disease. Given the adverse consequences of sustained and severe anemia, and the recent finding that blood transfusions appear to be beneficial rather than detrimental to patients undergoing renal transplantation [52], we transfuse packed red blood cells liberally in any patient at risk who has symptomatic anemia. Unfortunately, blood transfusions have untoward consequences, including an increased incidence of HBsAg hepatitis, but red cells properly screened for HBsAg and prepared by washing might reduce this risk. Increased iron stores also have been demonstrated in patients on chronic dialysis, but morbidity and mortality related to hemochromatosis have not yet been documented.

Uremic patients have compromised immune systems, and an increased frequency of infection has been reported [53]. Although hemodialysis tends to correct this immune deficiency, dialysis patients still seem to have an increased incidence of infection. For instance, patients with acute renal failure are particularly prone to septicemia, which is the most common cause of death in this group [30, 54]. The immune mechanisms might be depressed in patients with renal failure for a number of other reasons as well. Diverticulosis occurs commonly in chronic dialysis patients, especially those with polycystic kidney disease, and often is complicated by diverticulitis. In our program, these complications have led to an increase in intraabdominal infections. The high incidence of urinary tract abnormalities in these patients leads to an increased rate of urinary tract infection. Patients being dialyzed after renal transplantation also contract more infections, which likely are related to immunosuppressive therapy and not to uremia or dialysis. This association should prompt early reduction or cessation of immunosuppressive therapy in patients destined to return to chronic dialysis. Hemodialysis patients also have an increased incidence of elevated cytomegalovirus titers [55], and CMV infection probably causes pericarditis. Non-A, non-B hepatitis and "fevers of unknown origin" occur commonly in these patients. When dialysis patients develop type-B hepatitis, symptoms of liver involvement are typically lacking and the only manifestation is antigenemia. Although prevalence rates as high as 50% have been reported in some dialysis units, the rate of antigenemia in many programs is less than 5% [56]. The incidence of chronic hepatitis and cirrhosis seems low in dialysis patients, but Prison, Alexandre, and van Ypersele suggested that cirrhosis and hepatic failure occur at a higher rate in HBsAg-positive patients who undergo renal transplantation than in HBsAg-negative patients [57]. Of course, exposure of blood from patients with chronic antigenemia to nurses, physicians, and other patients poses a major problem.

Pericarditis occurs at two different periods in patients with kidney failure. First, it often occurs just prior to, or soon after, the induction of dialysis. In contrast to what happened to the patient presented, the pericarditis usually disappears without sequelae in patients who are dialyzed adequately. Second, pericarditis can occur in patients who are dialyzed chronically. In this setting, it can result from viral infection or an underlying systemic disease. Recently, Gelfand et al reported an increased incidence of pericardial effusion in uremic patients being treated with minoxidil [58]. This drug might have contributed to the effusion in the patient presented today. Pericarditis occurs most often in chronic dialysis patients concurrently with stress such as surgery, trauma, or infection. These patients, who are hypercatabolic, can manifest a "relative" uremia that results in pericarditis if the dialysis regimen is not increased. Some clinicians reduce the frequency and duration of dialysis treatments if a concurrent illness develops; I believe that one should not reduce the dialysis regimen but should increase the duration and frequency of treatment. For the patient with a pericardial friction rub, peritoneal dialysis can be considered. In my experience, however, hemodialysis has the advantage of increasing clearance, and it can be continued safely if anticoagulation is modified by reduction of the heparin dose through infusion, fractional dosage, or the use of carefully controlled regional heparinization. Pericardial effusion will develop, nonetheless, in a small number of patients but usually resolves with conservative therapy [59]. In the rare patient who develops cardiac tamponade, we have performed pericardiocentesis utilizing intrapericardial air infusion (Fig. 1). The procedure is performed by an experienced thoracic surgeon and may be repeated as many as three times. The quantity of air infused is approximately three-fourths the volume of fluid removed. To ensure that air is injected into the pericardial sac, simultaneous peripheral and pericardial hematocrits are determined, and the fluid removed is observed for absence of clotting. If location of the catheter is still not obvious, a small amount of Decholin® is injected through the catheter, and the patient immediately ex-

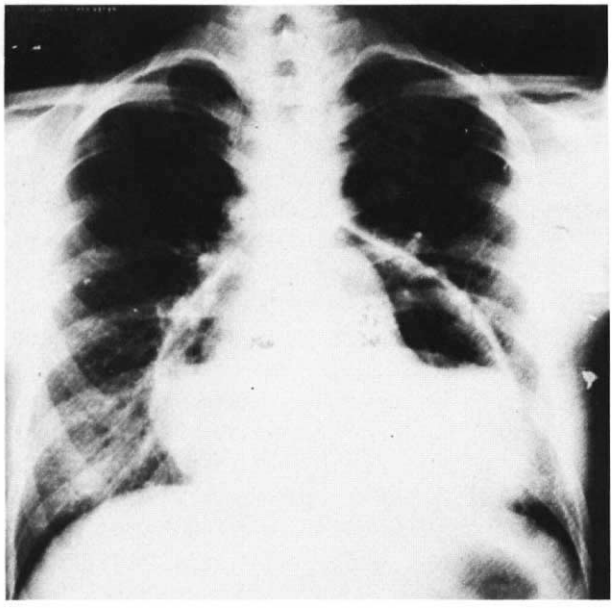

Fig. 1. *Chest radiograph showing intrapericardial air injected after pericardiocentesis.*

periences a sweet taste if the catheter tip is in an atrial or ventricular chamber. Administration of a non-absorbable steroid intrapericardially [60] and oral indomethacin [61] have been reported as beneficial and are sometimes used in conjunction with air instillation. Early pericardiectomy has been advocated because it produces little mortality [62, 63]. However, pericardiocentesis is a much less invasive procedure that offers considerably less morbidity. Over the past 10 years, in our large dialysis population, intrapericardial air infusion has avoided thoracotomy and led to resolution of effusion and tamponade without mortality or significant morbidity [64].

Some researchers have reported an acceleration of atherosclerotic cardiovascular disease in uremic patients on dialysis [65], but one recent study argues that atherosclerosis is not accelerated in this population [66]. Failure to define the population under consideration might explain the divergent results. If one considers entire dialysis populations, including patients of all ages and those with a long history of hypertension, then the incidence of atherosclerotic disease is, in fact, increased [3]. If one examines only young dialysis patients who have no history of hypertension or other risk factors, no increase in the incidence of atherosclerotic coronary artery disease is apparent. Longer follow-up is necessary to determine whether dialysis or "partially" treated uremia are factors in the pathogenesis of early atherosclerotic disease.

The literature on secondary hyperparathyroidism in patients on maintenance dialysis is extensive, and many approaches to prevention and treatment are described elsewhere. Hyperparathyroidism does not respond to hemodialysis alone. Diet and aluminum-containing antacids should be used to reduce the serum phosphorus level. Vitamin D analogues can be administered to maintain normal vitamin D metabolism and calcium absorption which, with dialysate calcium of 3.25 to 4.0 mEq/liter, will maintain modestly elevated serum calcium concentrations in the hope of preventing or reversing secondary hyperparathyroidism. In the patient with far advanced hyperparathyroidism, subtotal parathyroidectomy is sometimes necessary [67]. In patients not treated appropriately, the end results can include severe proximal myopathy; severe bone disease with pathologic fracture and pain; and subcutaneous, joint, visceral, and vascular calcification [68–73].

Several types of encephalopathy can occur in patients undergoing chronic dialysis [74]. Uremic encephalopathy is common in patients with advanced renal insufficiency, and mild forms can appear in inadequately dialyzed patients. A severe encephalopathy consisting of myoclonic jerking, speech impairment, dementia, and status epilepticus leading to death has been recognized in long-term dialysis patients [75]. The cause of this so-called "dialysis dementia" is unknown. Some researchers have suggested that orally administered alumimun gels cause the syndrome [76], but the sporadic nature of the disorder and its presence in only small numbers of patients taking oral aluminum suggest that some other factor might contribute to its pathogenesis. Others have indicated that the syndrome is related to aluminum in water used for dialysis [77]. One must distinguish the syndrome from atherosclerotic cerebral vascular disease in the diabetic or elderly patient. Dementia or unexplained neurologic findings in any patient on hemodialysis should suggest to the physician the possibility of subdural hematoma [78].

Many chemical abnormalities can persist in patients on chronic dialysis, including hyperlipidemia, mild acidosis, hyperuricemia, hypermagnesemia, hyperamylasemia, and elevated BUN and serum creatinine levels. The importance of these findings is unknown. Hypertriglyceridemia and decreased high-density lipoprotein levels might contribute to premature atherosclerotic disease; hyperuricemia might provoke gouty arthritis; and chronic acidosis probably accentuates metabolic bone disease. Al-

though high levels of BUN and serum creatinine usually are associated with symptoms in uremic patients who have not undergone dialysis, elevated values occur in chronic dialysis patients and are not associated with any obvious clinical problems. The BUN and serum creatinine can be quite high in patients with a large body mass, increased tissue catabolism, or high protein intake. A change in BUN and serum creatinine levels in such patients is a more important clue to an underlying problem.

Other problems, most of undetermined cause, continue to plague patients on chronic dialysis. Pruritis is common and often is severe and unrelenting. Several therapies have been recommended, although none seems very effective over the long term. Ultraviolet light therapy is of short-term benefit [79]. Patients, particularly the elderly, frequently complain of insomnia and fatique. The psychiatric, emotional, and social problems that occur in dialysis patients are too extensive to be discussed here but are major complications in this population. Finally, many serious complications result from the use of inappropriate drugs and dosage levels in dialysis patients. The physician must have an exact knowledge of the pharmacodynamics of each drug used in a patient with renal failure.

Hemodialysis is often lifesaving in patients with renal failure, but it has many potential side effects, some of which are lethal. Patients on hemodialysis should be monitored vigilantly, and their treatment should be modified to minimize the occurrence of complications. In any patient being considered for long-term therapy with hemodialysis, the potential risks and benefits of this complex treatment should be weighed carefully before therapy is initiated.

Questions and answers

DR. JOHN T. HARRINGTON: Dr. Lazarus, thank you very much for an encyclopedic review of the complications of dialysis, many of which this patient experienced. One of his major problems was pericarditis which, because it occurred soon after the initiation of dialysis, was probably due to uremia, not lupus. It seems to me, however, that some patients develop pericarditis months after dialysis has begun and when they are apparently "well dialyzed." What is the cause of pericarditis in this small group of patients?

DR. LAZARUS: The term "well dialyzed" is relative. There are many instances in which stable dialyzed patients develop increased catabolism secondary to other illness or surgery and then become relatively uremic. I believe that this phenomenon is probably the most common cause for pericarditis in the patient receiving maintenance dialysis. Occult causes of "under dialysis" also might be due to recirculation or inadequate blood flow from a poorly functioning shunt or fistula. The most common cause for pericarditis in a truly well-dialyzed patient probably is viral infection.

DR. JEROME P. KASSIRER: How many long- and short-term complications develop in patients you would consider adequately dialyzed? That is, what fraction of well-dialyzed patients remain free of complications?

DR. LAZARUS: Your question is difficult to answer with an exact percentage. Certainly, the patient's age and systemic disease are important factors in the development of complications. The most common complications, as I mentioned, are related to shunt and fistula difficulties. Continuing hypertension, progressive secondary hyperparathyroidism, and persisting anemia also are common and complicate the older patient's course. Significant mechanical complications should be very rare. In relatively healthy young people on hemodialysis, I find the incidence of complications quite low, but again, I cannot give you an exact percentage. Many of these younger patients live comfortably for many years. The complication rate in the young patient is sufficiently high, however, that transplantation should be seriously considered as a means of restoring normal renal function. Of course, one also must consider complications from that therapy as well.

DR. ROBERT RUBIN *(Chief of Nephrology, Lemuel Shattuck Hospital, Boston, Mass.):* Dr. Lazarus, you noted that cytomegalovirus infection is fairly common and that it might cause pericarditis in many of these patients. Have you examined CMV antibody levels in these patients?

DR. LAZARUS: Pericarditis occurring in stable dialysis patients actually is not common. In patients whose pericarditis is not due to the causes mentioned above, we have assumed the pathogenesis to be cytomegalovirus because of a lack of another cause and the clinical presentation. Many chronic dialysis patients have elevated CMV titers prior to an episode of pericarditis; therefore, it is necessary to demonstrate a change in titer. We have seen a significant elevation in titer in three patients with otherwise unexplained pericarditis.

DR. RUBIN: How do you evaluate patients who develop hypotension during hemodialysis?

DR. LAZARUS: A number of things can cause hypotension in patients during hemodialysis. I think the most common cause is removal of vascular vol-

ume faster than the patient's vascular system allows. Primary considerations influencing fluid removal are the size of the dialyzer and the rate of ultrafiltration. Contributing factors include a change in plasma osmolality, accumulation of acetate, and underlying autonomic neuropathy. It has been suggested that hypokalemia might play a role in hypotension. However, unless an arrhythmia is induced, I doubt its contribution. An underlying reduction in cardiac reserve is probably the major contributing cause. As I mentioned earlier, the use of antihypertensive medications accentuates hypotension during dialysis. Whether hormonal abnormalities, such as the absence or removal of dopamine beta-hydroxylase, catecholamines, or prostaglandins, affect hypotension during dialysis remains speculative at this time. Initially, I evaluate the appropriateness of volume reduction, and repair the volume deficit if necessary. This approach often resolves the problem. Because cardiac status is very fragile in some patients, dialysis using a low blood-flow rate and gentle ultrafiltration must be employed. Hyperosmolar agents such as mannitol, dextrose, and glycerol have been advocated by some to reduce hypotension. We have used dopamine or metaraminol (Aramine®) during ultrafiltration in the fluid-overloaded patient who also has hypotension. One can decrease extracellular volume with this manipulation, but as dialysis is stopped and the pressor agent is discontinued, the patient can again become hypotensive.

DR. WILLIAM B. SCHWARTZ *(Professor of Medicine, Tufts University School of Medicine, Boston, Mass.):* Could you comment further about the acetate problem and the problem of bicarbonate depletion in dialysis patients?

DR. LAZARUS: As I mentioned earlier, it was demonstrated a number of years ago that acetate can accumulate in a small percentage of patients on dialysis [17, 18]. Patients with hepatic disease seem to be particularly prone to this problem, but the abnormality also occurs in patients who have no apparent hepatic insufficiency. Several investigators have demonstrated a transient decrease in plasma bicarbonate concentration during and just after hemodialysis. Sargent and Gotch in an elaborate study demonstrated that body bicarbonate stores can be depleted after long periods of acetate hemodialysis [16]. Although the exact cause of acetate accumulation has not been well studied, acetate excess must result from *(1)* a rate of acetate presentation that exceeds the metabolic clearance; *(2)* a reduction in acetate delivery to active metabolic sites because of circulatory insufficiency; or *(3)* a defect in acetate metabolism. I am not aware of studies that have investigated further the exact mechanism of acetate metabolism in hemodialyzed uremic patients.

DR. HARRINGTON: The plasma bicarbonate concentration is 15 to 17 mEq/liter in most patients dialyzed against acetate, whereas patients who have been dialyzed against bicarbonate have higher plasma bicarbonate concentrations. I believe the "defect" in the acetate metabolism is best defined quantitatively. Twenty-four hours after acetate dialysis, the acetate level is not elevated; acetate accumulates only during the dialysis itself. Tolchin et al demonstrated that accumulation of acetate levels is most marked in patients being dialyzed with large-surface-area dialyzers (2.5 m^2); serum acetate levels rose to 5 to 10 mM/liter in these patients. It is of interest, however, that none of these patients developed significant hypotension [14].

DR. JORDAN J. COHEN: You emphasized that persistent hypervolemia is hard to detect in the dialysis patient and alluded to the frequently observed diuresis after successful transplantation. Has post-transplant diuresis been studied systematically to assess how much extra fluid is typically present in an apparently well-dialyzed patient?

DR. LAZARUS: I am not aware of a study of extracellular or vascular volume status before and after successful transplantation. I think most nephrologists appreciate this phenomenon, however.

DR. NICOLAOS MADIAS *(Renal Service, NEMCH):* As you know, several people believe that we wait too long before starting dialysis. Some European nephrologists, for example, suggest that we probably should start dialysis when the glomerular filtration rate reaches 15 to 20 cc/minute. They reason that waiting until the GFR reaches very low levels is unwise because of the multiple physiologic derangements that result. In view of the complications you have just reviewed, when do you think dialysis should be begun?

DR. LAZARUS: Timing of the initiation of dialysis is a difficult issue. I do not believe there is an absolute level of renal insufficiency that determines when dialysis should be started. Clearly, if one waits until the patient has neuropathy, pericarditis, severe central nervous system disease, or other serious complications of uremia, one has waited too long. I believe that dialyzing patients with a clearance of 15 to 20 cc/minute is not justified, however, because the risk at this level outweighs the benefits. Patients with slowly progressive renal insufficiency should be monitored regularly, and dialysis should

be started when the patient experiences a significant change in the quality of life. If the patient is symptomatic and cannot function normally, and if the problem is not correctable by conservative measures, then hemodialysis should be started regardless of the serum creatinine and BUN levels. On the other hand, many of us treat patients whose serum creatinine levels are as high as 18 to 20 mg/dl and whose urea nitrogen levels approach 200 mg/dl yet who have few physical findings or symptoms. With *careful follow-up,* these patients can be managed conservatively. It is interesting that diabetics commonly become symptomatic with relatively low BUN or serum creatinine levels.

Early transplantation is also a reasonable therapeutic consideration prior to the final stage of chronic renal insufficiency. While I was at the Childrens Hospital Medical Center, we transplanted kidneys in children early in the course of renal insufficiency in an effort to obtain normal renal function and achieve improved growth [80]. In the older patient with a well-matched kidney from a willing sibling, early transplantation again is worth considering.

DR. COHEN: You emphasized the frequency of CMV infections. Is there any prospect of immunization against this virus?

DR. LAZARUS: I know of no efforts to develop immunization against cytomegalovirus. In the dialysis patient, the problem might not be sufficient to warrant its routine use. The problem of CMV infection in transplant patients, however, is another issue; immunization might be important in that situation.

DR. SANG CHO *(Chief, Transplant Surgery, NEMCH):* Control studies of interferon are being carried out at this time by the renal transplantation group at the Massachusetts General Hospital [81]. The data suggest that interferon might reduce both the incidence and intensity of infection. It was my impression that CMV immunization would require a live, attenuated virus, which would impose a risk on transplant and dialysis patients, who are immunosuppressed and might not be able to tolerate a live virus vaccine.

DR. COHEN: At one time nerve conduction velocity tests were popular as a means of assessing the adequacy of dialysis. Do you find these studies still valuable?

DR. LAZARUS: The motor nerve conduction velocity study is a delicate test that must be performed appropriately, and room temperature, proper position of patients, and proper technique by the examiner must be taken into account. The test can have wide variability in the same patient, particularly a uremic patient who has neuropathy. Because nerve conduction velocity in uremic patients often is prolonged, isolated studies in dialysis patients are not helpful [82], and the clinical evaluation often can be just as rewarding as the nerve conduction velocity test. A trend in nerve conduction velocity over a long period, however, sometimes provides valuable information. We currently use serial nerve conduction velocity studies as a tool in evaluating the adequacy of dialysis. Neurobehavioralists are now evaluating psychologic tests that they believe might prove more valuable in assessing the adequacy of dialysis [83].

DR. COHEN: You emphasized the problem of bleeding in dialysis patients due to their requirement for anticoagulation. Are any new strategies being developed that might reduce that complication?

DR. LAZARUS: Yes, several drugs are being evaluated. Prostacyclin and ticlopidine, two agents that affect platelet adhesiveness, are being evaluated. In trying to prevent clotting without using systemic anticoagulation, some researchers have tried to attach heparin to dialysis membranes, but these attempts have not been successful, primarily because heparin is released from the membrane. At present, systemic anticoagulation with heparin remains a necessity for hemodialysis.

DR. MARTIN GELMAN *(Renal Division, St. Elizabeth's Hospital, Boston, Mass.):* I would like to return to the pericarditis issue. Your data supporting nonoperative intervention in patients with pericarditis are very impressive. Other researchers, such as those in Minnesota, believe that surgery is virtually always necessary [60]. Do you think air instillation makes the difference?

DR. LAZARUS: I believe so. A number of papers in the last five years have advocated early pericardiectomy as the procedure of choice for pericardial effusion because pericardiectomy is a safe operation [62, 63]. This might be true; however, just because an operation is safe does not make it necessary. We have had no difficulties with pericardiocentesis, primarily because the procedure is performed in our institution by an experienced thoracic surgeon. The use of echocardiography has been valuable in this regard. Intrapericardial air allows a more thorough drainage of fluid, gives immediate pain relief, and prevents reaccumulation of significant fluid. The use of nonabsorbable steroids in the pericardium has been reported by the Minnesota group as being effective also [60]. We have not

had to resort to thoracotomy and pericardiectomy in the treatment of pericardial tamponade.

DR. HARRINGTON: Have you had any problems with the late sequelae of pericardial effusion such as constrictive pericarditis?

DR. LAZARUS: During the past 12 years, 2 of our patients have developed constrictive pericarditis. One was a home-dialysis patient who developed the syndrome 6 to 8 weeks after having had pericarditis without pericardial effusion. The other was an elderly patient whose constrictive pericarditis occurred approximately 2 years after a pericardial effusion that cleared spontaneously. Neither of these patients had required pericardiocentesis earlier. The incidence of constrictive pericarditis is quite low. I do not believe that the possibility of constrictive pericarditis warrants early pericardiectomy, as the incidence is low and the procedure can be done when constriction is demonstrated.

DR. GELMAN: What is the overall incidence of effusion in your patients? Are pericardial effusions recurrent in this group?

DR. LAZARUS: We screened a population of patients on maintenance dialysis who had no symptoms, and we found an incidence of anterior pericardial effusion of approximately 20% [84]. Other groups have performed serial studies indicating that pericardial fluid accumulation is evanescent [85].

Reprint requests to Dr. J. Michael Lazarus, Nephrology Division, Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston, Massachusetts 02115, USA

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